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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,057	01/28/2004	Roy H. Larsen	50147/003002	2306

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

NOTIFICATION DATE	DELIVERY MODE
08/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/766,057	LARSEN ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/21/10 has been entered.

Claims and Previous Rejections Status

2. Claims 18 and 25-35 are pending in the application.

3. The rejection of claims 18 and 25-35 under 35 U.S.C. 103(a) as being unpatentable over Wedeking et al. (US 6,093,382) in view of Sinkule et al. (EP 282057) is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 18 and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wedeking et al. (US 6,093,382) in view of Sinkule et al. (EP 282057).

6. Wedeking et al. (US 6,093,382) discloses the method of preparing a diagnostic/therapeutic gadolinium-folate (folic acid) conjugate and the method of targeting the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein) (i.e. malignant cells) which involves administering the conjugate to a mammal and monitoring the biodistribution (column 1, lines 8-50; column 6, lines 28+; column 7, lines 21-28 and 48-59; column 8, line 44-59; column 10, lines 18-25; column 68, lines 31+; example 17). The compound of column 51-52 contains multiple folates (folic acid) conjugated to a radionuclide chelator capable of binding gadolinium. FBP is frequently strikingly elevated in a variety of carcinomas and thus allows for selective concentration of pharmaceutical or diagnostic agents in tumor cells, such as ovarian cancer relative to normal cells (column 3, lines 25-35; column 4, lines 37-54; column 5, lines 1-7). The monomeric folate conjugates of Gd chelates designed for use in MR applications indicate that structural modifications that bring about an increase in the intensity of the MR signal are advantageous, as the signal intensity obtainable with this technique is determined by the quantity of paramagnetic or superparamagnetic metal that can be localized in the target tissues which is limited by the quantity of folate binding protein present in those tissue (column 7, lines 21-38). Wedeking et al. does not disclose the coupling of an antibody to the folate gadolinium-folate (folic acid) conjugate.

7. Sinkule et al. (EP 282057) discloses the method of monitoring the biodistribution of a receptor binding conjugate comprising three components, 1.) a monoclonal antibody, IgG (column 2, lines 30-31; example 4), 2.) a radionuclide (column 3, lines 39-

55; column 17, lines 5-17) a chemotherapeutic agent, such as folate analogues and multiples thereof (abstract; column 2, lines 11-14 and 29-30; column 4, lines 18-28) via the administration to a mammalian (i.e. intravenous) (column 6, lines 19+). The method of linking the folic acid derivative to an antibody involves conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride and mixing it with the antibody (column 8, lines 40-44). The antibody-folic acid derivative product is further attached to a radionuclide (column 6, lines 22-25). The antibody may be a monoclonal, polyclonal or variations thereof used for a wide variety of target antigens (column 3, lines 56+; column 4, lines 9-15), such as (443A6) which recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas (column 8, lines 33-39; example 3). The targeting antibodies are included in the conjugate to target the conjugate to a desired tumor cell for uptake with a high degree of specificity which facilitates the destruction of cancerous cells while minimizing the damage to normal cells (column 5, lines 9-12 and 22-47) an the choice of antibody will depend on the type of cancer with which the patient is afflicted (column 5, lines 40-47).

8. At the time of the invention it would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Sinkule et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific

targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

9. The IgG of the disclosure encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties.

Response to Arguments

10. Applicant's arguments filed 7/13/10 have been fully considered but they are not persuasive.

11. Applicant asserts that Sinkule does not teach "that IgG can be successfully used to target desired tumor cells upon conjunction to a radionuclide-folate analogue species without interfering with folate targeting because Sinkule fails to disclose targeting the conjugate to a malignant cell using the folate component of the complex. Instead, Sinkule explicitly states that the antibody component targets the complex to the tumor.

12. The antibody targeting/binding of the radionuclide-folate analogue complex of Sinkule does not exclude simultaneous and/or synergistic folate targeting/binding.

13. The IgG of Sinkule et al. encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties.

14. Applicant asserts that while the conjugate of Sinkule may contain folic acid analogues, these folic acid analogues are described as chemotherapeutic agents,

15. The instant claims recite, “non-cytotoxic folate to form a dual binding conjugate". The folic acid analogues (chemotherapeutic agents) of the disclosures encompass the non-cytotoxic folate of the instant claims and therefore have the same properties and are capable of the same functions, such as forming a dual binding conjugate.

16. Further, the instant claims do not exclude that the non-cytotoxic folate is a chemotherapeutic agent.

17. Applicant assets that adding a large molecule, such as BSA, to a folate-containing complex, can interfere with the targeting ability of the folate.

18. The instant claims are not drawn to the method of folate targeting of the folate-containing complex.

19. BSA is not structurally or chemically identical to IgG and thus does not exactly replicate IgG's actions/interactions in vivo. Further, the IgG of Sinkule et al. encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties.

20. Also, the antibody targeting/binding of the radionuclide-folate analogue complex of Sinkule does not exclude simultaneous and/or synergistic folate targeting/binding.

21. Applicant asserts that the dual binding ability of the conjugates encompassed by the present claims is neither taught nor suggested by Sinkule.

22. The antibody targeting/binding of the radionuclide-folate analogue complex of Sinkule does not exclude simultaneous and/or synergistic folate targeting/binding.

23. The IgG of Sinkule et al. encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties.

Conclusion

24. No claims are allowed at this time.

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618